PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Artcle 36 and Rule 70)

Applicant's or agent's file reference OF03P067	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. **PCT/KR2003/000882**	International filing date *(day/month/year)* **01 MAY 2003 (01.05.2003)**	Priority date *(day/month/year)* 02 MAY 2002 (02.05.2002)

International Patent Classification (IPC) or national classification and IPC

IPC7 A61K 31/133

Applicant

DOOSAN CORPORATION et al

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicabiiity
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

접수 2004. 3. 16 법무법인 케이씨엘

Date of submission of the demamd	Date of completion of this report
21 NOVEMBER 2003 (21.11.2003)	11 AUGUST 2004 (11.08.2004)

Name and mailing address of the IPEA/KR	Authorized officer
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Form PCT/IPEA/409 (cover sheet) (July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International aplication No.
PCT/KR2003/000882

I. Basis of the report

1. With regard to the elements of the international application:*

- [X] the international application as originally filed
- [ ] the description:
  - pages _____ , as originally filed
  - pages _____ , filed with the demand
  - pages _____ , filed with the letter of _____
- [ ] the claims:
  - pages _____ , as originally filed
  - pages _____ , as amended (together with any statment) under Article 19
  - pages _____ , filed with the demand
  - pages _____ , filed with the letter of _____
- [ ] the drawings:
  - pages _____ , as originally filed
  - pages _____ , filed with the demand
  - pages _____ , filed with the letter of _____
- [ ] the sequence listing part of the description:
  - pages _____ , as originally filed
  - pages _____ , filed with the demand
  - pages _____ , filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language English which is

- [ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- [X] the language of publication of the international application(under Rule 48.3(b)).
- [ ] the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/ or 55.3).

3. With regard to any **nucleotide** and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- [ ] contained inthe international application in written form.
- [ ] filed together with the international application in computer readable form.
- [ ] furnished subsequently to this Authority in written form.
- [ ] furnished subsequently to this Authority in computer readable form
- [ ] The statement that the subsequently furnished written sequence listing does not go beyond the disc losure in the international applicationas as filed has been furinshed.
- [ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. [ ] The amendments have resulted in the cancellation of:
   - [ ] the description, pages _____
   - [ ] the claims, Nos. _____
   - [ ] the drawings, sheet _____

5. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box(Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed." and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION

International aplication No.
PCT/KR2003/000882

V. **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-13	YES
	Claims		NO
Inventive step (IS)	Claims	1-8, 10, 11	YES
	Claims	9, 12, 13	NO
Industrial applicability (IA)	Claims	1-13	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The following documents are referred to in this report; the numbering will be adhered to in the rest of the procedure:

D1: FEBS Letters, 2001, 499(1/2), pp.82-6

D2: WO 00/53568 A

D3: Advanced organic chemistry, 4th edition, Wiley-Interscience Publication, Jerry March, 1992, pp.898-901

The present invention relates to a composition comprising dimethylphytosphingosine which has an inhibitory activity of sphingosine kinase, an inhibitory activity of protein kinase C(PKC), an apoptosis inducing activity, a treating activity of hyperplastic disease, an anti-cancer activity and an anti-bacterial activity.

D1 discloses that phytosphingosine and N-acetyl phytosphingosine exert strong cytotoxic effects on Chinese hamster ovary (CHO) cells and greatly inhibit the phospholipase D activity.

D2 discloses antimicrobial and anti-inflammatory composition containing organic acid salt of phytosphingosine.

D3 discloses that primary amines are reductively methylated with formaldehyde and reducing agent.

1. Novelty

Since none of these documents disclose a composition comprising dimethylphytosphingosine, the subject matter of the present invention is novel over D1 to D3.

(Continued on Supplemental Sheet)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of:

Box V.

2. Inventive Step

(1) Claims 1-8, 10-11

Claims 1-5 and 10-11 of the present invention relate to an anti-cancer composition comprising dimethylphytosphingosine, a kit for treating cancer comprising the above composition and a composition for treating a hyperplastic disease comprising dimethylphytosphingosine. Claims 6-8 of the present invention relate to a sphingosine kinase inhibitor, apoptosis inducing and protein kinase inhibitor composition comprising dimethylphytosphingosine as an active ingredient.

D1 discloses phytosphingosine and N-acetyl phytosphingosine which have strong cytotoxicity effects on CHO cells and inhibitory effect on phospholipase D.
However, no particular relationships present between the inhibitory activity against phospholipase D, cytotoxicity on a CHO cell(a normal cell) and an apoptisis, so the anti-cancer activity and the apoptosis inducing activity of dimethylphytosphingosine are not obvious to a person skilled in the art.

Therefore, the subject matter of claims 1-8, 10-11 is regarded to be inventive over D1.

(2) Claims 9, 12

Claims 9, 12 relate to an anti-inflammatory and antibacterial composition comprising dimethylphytosphingosine as an active ingredient. D2 discloses an antimicrobial and anti-inflammatory composition containing organic acid salt of phytosphingosine.

The present invention is different from D2 only in that the present invention uses dimethylphytosphingosine as an active ingredient, whereas D2 uses organic acid salt of phytosphingosine as an active ingredient. However, it is obvious to a person skilled in the art to modify organic acid salt of phytosphingosine to dimethylphytosphingosine by N-dimethylation of phytosphingosine. Therefore, claims 9, 12 are considered to lack an inventive step.

(3) Claim 13
Claim 13 relates to a precess for producing N,N-dimethylphytosphingosine comprising the reaction of phytosphingosine with formaldehyde in the presence of a reducing agent via N-monomethylphytosphingosine as an intermediate.
As reductive dimethylation of primary amine with formaldehyde and the reducing agent is obvious to a person skilled in the art as shown in D3, claim 13 is considered to lack an inventive step.

3. Industrial Applicability
Claims 1-13 are considered to be industrially applicable.